Randomized controlled clinical study comparing a volume-stable collagen matrix to autogenous connective tissue grafts for soft tissue augmentation at implant sites: linear volumetric soft tissue changes up to 3 months

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Abstract: AIM: To test whether or not the use of a volume-stable collagen matrix (VCMX) results in soft tissue volume increase at implant sites non-inferior to an autogenous subepithelial connective tissue graft (SCTG). METHODS: In 20 patients, soft tissue augmentation at implant sites was performed using VCMX or SCTG. Casts obtained prior to augmentation (BL), at 30 (FU-30) and 90 days (FU-90) were digitized and transferred to stereolithography (STL) files. BL, FU-30 and FU-90 STL files were superimposed and linear volumetric changes evaluated in crestal and buccal regions of interest (ROI). Descriptive analysis was computed for both groups and a test for non-inferiority was performed. RESULTS: The median linear changes from BL to FU-90 in the crestal ROI amounted to 0.175 mm (0.06; 0.51) for VCMX (p = 0.002 over time) and to 0.51 mm (0.23; 0.94) for SCTG (p = 0.129). The differences between the two groups were not significant (p = 0.287). The respective values in the buccal ROI were 0.59 mm (0.26; 1.06) for VCMX (p = 0.002) and 0.94 mm (0.66; 1.13) for SCTG (p = 0.004). The differences between the two groups were not significant (crestal: p = 0.287; buccal: p = 0.534). Non-inferiority could be concluded for VCMX compared to SCTG for both ROI. CONCLUSION: VCMX and SCTG can be used for soft tissue augmentation at implant sites resulting in an at least short-term increase in volume.

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Randomized controlled clinical study comparing a volume-stable collagen matrix to autogenous connective tissue grafts for soft tissue augmentation at implant sites: linear volumetric soft tissue changes up to 3 months

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Running title: volumetric changes at implant sites

Key words: soft tissue augmentation, soft tissue volume, collagen-based matrix, subepithelial connective tissue graft, dental implant

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CONFLICT OF INTEREST AND SOURCE OF FUNDING STATEMENT

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CLINICAL RELEVANCE

Scientific rationale for the study: Soft tissue volume augmentation is frequently performed in the esthetic zone to optimize the soft tissues quantity prior to the insertion of the final reconstruction. Up to date, the use of autogenous subepithelial connective tissue grafts (SCTGs) is considered to be the gold standard for such interventions. A recently developed volume stable collagen matrix (VCMX) demonstrated favorable properties in terms of soft tissue volume increase based on preclinical studies. This clinical study aimed to compare the volumetric soft tissue changes utilizing VCMX with the use of SCTG.

Principal findings: Soft tissue augmentation using VCMX resulted in a soft tissue volume increase non-inferior to the use of SCTG at implants sites in the esthetic zone.

Practical implications: VCMX may serve as an alternative to SCTGs for the augmentation of soft tissue volume at implant sites.

ABSTRACT

Aim: to test whether or not the use of a volume stable collagen matrix (VCMX) results in soft tissue volume increase at implant sites non-inferior to an autogenous subepithelial connective tissue graft (SCTG).

Methods: In 20 patients soft tissue augmentation at implant sites was performed using VCMX or SCTG. Casts obtained prior to augmentation (BL), at 30 (FU-30) and 90 days (FU-90) were digitized and transferred to stereolithography (STL) files. BL, FU-30 and FU-90 STL files were superimposed and linear volumetric changes evaluated in crestal and buccal regions of interest (ROI). Descriptive analysis was computed for both groups and a test for non-inferiority performed.

Results: The median linear changes from BL to FU-90 in the crestal ROI amounted to 0.175mm (0.06; 0.51) for VCMX (p=0.002 over time) and to 0.51mm (0.23; 0.94) for SCTG (p=0.129). The differences between the two groups were not significant (p=0.287). The respective values in the buccal ROI were 0.59mm (0.26; 1.06) for VCMX (p=0.002) and 0.94mm (0.66; 1.13) for SCTG (p=0.004). The differences between the two groups were not significant (crestal: p=0.287; buccal: p=0.534). Non-inferiority could be concluded for VCMX compared to SCTG for both ROI.

Conclusions: VCMX and SCTG can be used for soft tissue augmentation at implant sites resulting in an at least short-term increase in volume.

INTRODUCTION

Esthetic demands of patients being provided with implant-borne fixed reconstructions have increased over the years. Moreover, the development of new materials, new technologies and enhanced knowledge of the periodontal and the peri-implant biology provide means to mimic the anatomical and esthetic characteristics of missing teeth. The delivered reconstructions should present a natural appearance and long-term functional, biological and esthetic stability of the implant site. On the level of the peri-implant tissues, objective parameters exist to evaluate the outcomes of implant therapy including the presence or absence of the papilla, the level of the mucosal margin as well as 2D and 3D changes of the peri-implant tissues (Furhauser et al., 2005). In case of volume deficiencies on the buccal side of dental implants, soft tissue augmentation surgery has been considered an integral part of implant therapy (Thoma et al., 2014b). Needs for soft tissue augmentation are based on the mucosal biotype and esthetic expectations. Thin peri-implant tissues are more prone to recessions, whereas a certain critical mucosal thickness has been suggested to avoid a discoloration of the peri-implant tissues (Jung et al., 2007, van Brakel et al., 2011, Thoma et al., 2016a). Moreover, soft tissue grafting contributes to more than 40% of the final volume at implant sites (Schneider et al., 2011), results in superior esthetics and more stable facial soft tissue dimensions in conjunction with immediate implants (Migliorati et al., 2015) and might contribute to more stable marginal bone levels at implant sites (Puisys and Linkevicius, 2015, Akcali et al., 2016). Most frequently, autogenous subepithelial connective tissue grafts (SCTGs) are used to augment soft tissue volume and according to the literature, are considered to be the gold standard (Thoma et al., 2009, Thoma et al., 2014a). However, the harvesting procedure is classified as being difficult and may be associated with the risk of intra- and postoperative complications such as bleeding, infection or necrosis (Del Pizzo et al., 2002, Soileau and Brannon, 2006). Therefore, research activities have focused on alternative devices to replace autogenous tissue and thereby eliminating the harvesting procedure. For such purposes, a volume stable collagen

matrix (VCMX) was developed. Based on in vitro and preclinical studies the matrix not only demonstrated favorable biological but also promising mechanical properties (Mathes et al., 2010, Thoma et al., 2011). In a canine study a volumetric analysis using a digital optical scanning and assessment method was applied to compare the efficacy of the VCMX regarding increase in soft tissue volume compared to the gold standard, the SCTG. It was concluded that the use of the matrix rendered a soft tissue volume increase non-inferior to SCTGs (Thoma et al., 2010). Analyses for volume changes were evaluated based on a non-invasive method using digitized models that were superimposed (Windisch et al., 2007). This techniques has proven to be reliable and has been used for a variety of clinical and preclinical studies (Fickl et al., 2009, Rebele et al., 2014, Schneider et al., 2011).

The aim of the present clinical study was to test whether or not the use of a volume stable collagen matrix (VCMX) results in a soft tissue volume increase at implant sites non-inferior to a subepithelial connective tissue graft (SCTG) over an observation period of 90 days.

Materials and Methods

Study design

This study was designed as a randomized controlled clinical trial and performed in accordance with the ISO Standard 14155:2011, clinical investigation of medical devices for human patients with the appendices VIII and X of the Medical Device Directive 93/42/EEC and with the Declaration of Helsinki, 2004. Upon approval by the local ethical committee (KEK-ZH-Nr 2011-0408), patients were recruited, informed consent obtained and screened for inclusion.

A detailed description of the inclusion/exclusion criteria and the clinical procedures is reported in a previous publication evaluating the same patient population with respect to the effectiveness and safety of the two treatment modalities (Thoma et al., 2016c). In brief, patients in need of soft tissue volume increase at single-tooth implant sites with two natural neighboring teeth were included. Main indications included: soft tissue contour deficit, buccal soft tissue thickness <2mm, shimmering of implants through the mucosa and thin biotype. Dental implants had to be placed between 6 weeks and 6 months prior to enrolment. Heavy smoking (> 10 cigarettes per day), probing pocket depths >4mm, insulin-dependent diabetes, general contraindications for dental and/or surgical treatment, allergy to collagen and pregnancy or breast feeding were considered as exclusion criteria.

Clinical procedures (Figure 1)

Due to the nature of the study evaluating the safety of a new soft tissue substitute, all patients were premedicated with 1.5g amoxicilline (Amoxicilline, Sandoz) as well as with 500mg mefenaminacid (Ponstan 500, Parke-Davis) for pain relief. Following administration of local anesthesia, a full thickness flap was elevated on top of the ridge and on the lingual side. Subsequently, a split flap was prepared at the buccal aspect resulting in a pouch for the transplant. At this time-point a sealed envelope containing the randomly assigned treatment modality was opened. Randomization was performed using a computer-generated list. Either the volume stable collagen matric (VCMX, test) or an autogenous subepithelial connective tissue graft (SCTG, control) were applied. In

group VCMX, the matrix was shaped to match the desired size in the recipient bed. In group SCTG, an autogenous connective tissue graft was harvested using a single incision technique according to standard techniques (Hurzeler and Weng, 1999). Subsequently, the graft (VCMX/SCTG) was positioned in the pouch and immobilized with a horizontal mattress suture to the lingual flap. Finally, primary wound closure was achieved with horizontal mattress and single interrupted sutures. Patients received prescriptions for analgesic and anti-inflammatory medications for three days (Ponstan®, Parke-Davis) and were instructed to rinse with a 0.2% solution of chlorhexidine (Hibitan®, Astra-Zeneca) twice a day for 10 days. Additionally, the patients were prescribed 2.25 g amoxicillin (Amoxicillin®, Sandoz) per day for 7 days.

Sutures were removed 7-10 days after the surgery and teeth were professionally cleaned with a mild abrasive prophylaxis paste. At 30 and 90 days post soft tissue augmentation, follow-up examinations were performed (FU-30; FU-90). In addition, at FU-90, a minimally invasive abutment connection was performed using a u-shaped incision design. The cover screw of the implant was removed, the small flap placed underneath the buccal pouch and a healing abutment connected to the implant.

Assessment of the linear volumetric changes

Prior to surgery (baseline), at FU-30 and FU-90, impressions of the grafted sites were taken including at least the two neighboring teeth and using an A-silicone impression material (President, Coltene/Whaledent). Dental stone casts were fabricated (Fujirock, Picodent) and optically scanned with a desktop 3D scanner (Imetric 3D, Courgenay, Switzerland). Digital models of each time-point per patient were captured as stereolithography (STL) files. Subsequently, these STL files were imported into a digital imaging software program (SMOP, Swissmeda, Zurich, Switzerland) for analysis of the volumetric changes in the grafted areas. The images of the baseline and follow-up datasets were superimposed and matched using the best-fit algorithm at the adjacent tooth surfaces. After definition of specific regions of interest (ROI) (Figure 2), the software calculated the volumetric changes measured in mm, which corresponded to the

mean distance between the three surfaces representing the evaluated time-points (BL, FU-30 and FU-90).

Regions of interest

Two regions of interest were defined. The crestal ROI had a trapezoid shape and was located at the crestal aspect of the grafted area determined by the midcrestal line and the gingival margins of the adjacent teeth (Figure 2a). The buccal ROI was characterized by a trapezoid shape and defined as the area between the gingival margins of the adjacent teeth, the mucogingival junction as apical and the interproximal areas as lateral borders (Figure 2b). Due to the individually variable anatomical situations, the measured area varied between patients, but was kept constant in each patient and site over time. All ROIs and measurements were performed by one examiner unaware of the treatment modalities.

Statistical analysis

Descriptive statistics including mean, median, standard deviation, quartiles and extreme values were used to describe the continuous parameters. In order to show that the two treatment groups did not differ relevantly with respect to the medians of change in soft tissue volume, a nonparametric non-inferiority test was performed at 1-sided significance level of 2.5% using an equivalence margin of 1mm using a nonparametric 95%-confidence interval. If the lower bound of the confidence interval was below the limit [-1 mm], a statement about non-inferiority was not possible. Otherwise, non-inferiority could be concluded. Within further analyses, differences between groups were evaluated with nonparametric methods, as the Mann-Whitney test and nonparametric 95% confidence intervals. The within group comparison to analyze the changes from baseline are based on the Wilcoxon signed rank test. The sample size calculation yielded 7 patients per group (total 14 patients) with a power of 93%, assuming a standard deviation per group of 0.5 mm, the conditions of the test as mentioned above. Taking

into account a drop-out rate of 30% for the primary endpoint 90 days (increase in soft tissue thickness), 10 patients per group were calculated.

RESULTS

A total of 20 patients entered the clinical trial having fulfilled all inclusion criteria. An overview on patient demographics and sites is given in table 1. Fifty-seven models of 19 patients were evaluated with respect to the volumetric changes in the grafted areas. One patient could not be included in the linear volumetric evaluation because of missing stone replicas.

The median crestal ROI was 24.8mm^2 (Q1:23.8; Q3:26.9) and 23.7mm^2 (21.2; 26.2) for VCMX and SCTG, respectively. The corresponding values for the buccal ROI were 32.2mm^2 (31.6; 33.1) for VCMX and 29.2mm^2 (24.6; 31.4) for SCTG. For both ROI, the differences between VCMX and SCTG groups were not statistically significant (crestal p= 0.278; buccal p=0.113).

The descriptive measures for the linear volume changes between BL, FU-30 and FU-90 are presented in table 2. Figure 3 represent two examples of linear volume changes for VCMX (left) and SCTG (right).

Linear volumetric changes from BL to FU-30

The median changes between BL and FU-30 revealed a significant increase in soft tissue volume of 0.41mm (0.24; 0.94) for VCMX (p=0.002) and a non-significant increase of 0.53mm (-0.02; 1.24) for SCTG (p=0.055) in the crestal ROI, and of 1.10 (0.54; 1.68) (p=0.002) and of 1.22 (0.59; 1.49) (p=0.004) in the buccal ROI for VCMX and SCTG, respectively. In both locations, the differences between the groups were statistically not significant (crestal p=0.826; buccal p=0.968).

Linear volumetric changes from FU-30 to FU-90

The median linear changes between FU-30 and FU-90 amounted to -0.29mm (-0.36; -0.21) for VCMX and -0.19mm (-0.31; -0.10) mm for SCTG at the crestal ROI. The change in the test group was statistically significant (p=0.006), whereas the change

in the control group was not statistically significant (p=0.055). In the buccal ROI the soft tissue volume decreased from FU-30 to FU-90 by -0.44mm (-0.59; -0.24) for VCMX and -0.15mm (-0.45; -0.09) for SCTG. The changes at the buccal ROI were statistically significant in the test group VCMX (p=0.002) but not in SCTG (p=0.016). The difference between the two groups did not differ significantly (p=0.675 crestal; p=0.287 buccal).

Volumetric changes from BL to FU-90 (primary outcome)

The median linear changes from BL to FU-90 in the crestal ROI amounted to 0.175mm (0.06; 0.51) for VCMX and to 0.51mm (0.23; 0.94) for SCTG. The change in the test group was significant (p=0.002), whereas the change in the control group was not significant (p=0.129) due to a larger standard deviation or inter-quartile range. The differences between the two groups did not differ significantly (p=0.287). The estimated lower limit of the one-sided 97.5% confidence interval of the location difference of the two groups was −0.74 mm by crestal soft tissue volume. Because −0.74 mm was above the $-\delta$ value of -1 mm, non-inferiority can be concluded for VCMX in comparison with the SCTG.

The median increase in soft tissue volume from BL to FU-90 in the buccal ROI was 0.59mm (0.26; 1.06) for VCMX and 0.94mm (0.66; 1.13) for SCTG. The change for VCMX was significant (p=0.002) as well as the change for SCTG (p=0.004). The differences between the two groups did not differ significantly (p=0.534). The estimated lower limit of the one-sided 97.5% confidence interval of the location difference of the two groups was −0.66 mm by buccal soft tissue volume. Because −0.66 mm was above the $-\delta$ value of -1 mm, non-inferiority could be concluded for the buccal ROI.

DISCUSSION

The current RCT demonstrated that i) the linear soft tissue volume at the crestal and buccal levels increased significantly up to the last follow-up using both treatment modalities; ii) the increase was more pronounced in the buccal than in the crestal region of interest; iii) the linear soft tissue volume decreased between 30 days and 90 days following the surgical intervention, sometimes significantly; iv) VCMX resulted in linear soft tissue volume changes non-inferior to SCTG in both regions of interest and for all analyzed intervals.

The assessment of volume changes using computer-assisted methods is an emerging tool in the field in dental research. A reason for might be that the analysis of a specific area gives more detailed information on the changes of the peri-implant tissues over time. Traditionally, transmucosal probing or ultrasonic assessment were most frequently applied to evaluate changes in soft tissue thickness (Eghbali et al., 2014, Migliorati et al., 2015). The volumetric analysis, however, has proven to be precise and reliable in vitro and in preclinical as well as in clinical studies (Fickl et al., 2009, Rebele et al., 2014, Schneider et al., 2011, Thoma et al., 2010, Windisch et al., 2007).

Although several techniques and materials were used to augment soft tissue volume around dental implants, data in terms of effectiveness and stability are scarce (Thoma et al., 2014b, Eghbali et al., 2014). In a prospective clinical study, the dimensional changes of the peri-implant tissues were evaluated, thereby analyzing the impact of each treatment step: implant placement and bone augmentation, soft tissue augmentation, and the insertion of the final prosthetic reconstruction (Schneider et al., 2011). A volumetric analysis was performed similarly to the analysis in the present study. The results indicated that soft tissue volume augmentation using a SCTG was effective and resulted in a volume increase of 0.55±0.53mm after 4 weeks. The soft tissue augmentation contributed to more than 40 % to the overall increase of peri-implant tissue volume in the buccal aspect between baseline and the delivery of the reconstruction (Schneider et al., 2011). These findings correlate with the results of the

present study demonstrating a significant increase from baseline to 30 days after soft tissue augmentation. For both treatment modalities, the mean increase in soft tissue volume was 0.8mm on the, from an esthetic point of view most important, buccal side of implant. These results are well in line with two recent clinical studies evaluating the horizontal stability of soft tissue volume augmentation with SCTGs at the buccal aspect of single implant sites (Eghbali et al., 2014, De Bruyckere et al., 2015). In both studies the soft tissue augmentation resulted in a significant increase in soft tissue thickness between 0.92 and 1.07 mm. In contrast to the present study, however, the soft tissue augmentation was performed after the insertion of the provisional reconstruction using an envelope technique. In addition, the soft tissue thickness was assessed using an ultrasonic device. Thus, this tool does not cover an entire area or volume (three-dimensional), but rather single entry points (two-dimensional) (Eghbali et al., 2014).

In contrast to the previously mentioned studies analyzing changes of the peri-implant tissues at the buccal aspects of the implant sites, the present study included another region of interest in the crestal area of the ridge, on top of the implant. Interestingly, for both treatment modalities the increase in soft tissue volume in this area was smaller compared to the buccal aspect from baseline to 30 days and to 90 days respectively. This finding might be explained with an increased pressure on the transplants in the crestal region caused by the primary wound closure and the location of the sutures. In contrast to SCTGs, which are relatively resistant to mechanical load, the VCMX features a high elasticity and appears to be more prone to compression forces. Consequently, a more pronounced volume difference was observed between the buccal and crestal region of interest in group VCMX. The effect of the suturing procedure on guided bone regeneration techniques was recently shown in an in-vitro study analyzing the volume stability pre- and post suturing (Mir-Mari et al., 2016). Depending on the stability of the regenerative materials, more or less volume loss occurred following suturing, with more favorable outcomes for techniques using volume-stable materials and/or some type of fixation (pins).

In the present study, 30% (VCMX) and 10% (SCTG) of the sites presented with a soft tissue dehiscence defect at the time of suture removal (Thoma et al., 2016c). Although the further healing was free of complications and complete wound closure was observed in all sites at 30 days, the healing by secondary intention resulted in a soft tissue invagination and thereby contributed to a loss of soft tissue volume, predominantly in the crestal region. The relatively high rate of dehiscences, specifically observed with the VCMX might to a great part be attributed to the learning curve. The VCMX had not been used previously in patients and no pilot clinical cases were performed. Due to the nature of the VCMX exhibiting a swelling rate of 20-30% following hydration (upon placement into the recipient site), flap release was crucial and might not have been appropriate in all cases. In addition, in previous experiments, various VCMX prototypes were analyzed (Mathes et al., 2010, Thoma et al., 2012). Based on these studies, a higher density and/or higher cross-linking of the matrix resulted in less cell infiltration and a reduced matrix stability. One might therefore speculate that in case the VCMX was compressed after wound closure in the present study, this could have negatively affected the obtained volume gain. The influence of dehiscences could, however, not be related to the outcome measures in the present study.

A decrease in soft tissue volume was observed between 30 days and 90 days following soft tissue augmentation for both treatment modalities. The loss of volume ranged between 0.24 and 0.39 mm and was, except for the crestal region of interest in the control group, statistically significant. These changes are well in line with a recently published preclinical study, demonstrating that implant sites augmented with SCTGs or VCMX underwent remodeling processes starting from 1 month after augmentation and continued up to 6 months (Thoma et al., 2016b). Dimensional changes following augmentation procedures predominantly occur during the initial phase of the wound healing due to remodeling processes. The most pronounced volume alterations take place within the first three months after soft tissue surgery (Studer et al., 2000). A

recently published randomized controlled clinical trial evaluated the effectiveness of two different techniques to augment soft tissue volume in ridge defects in the anterior maxilla and monitored the dimensional changes up to 6 months after soft tissue augmentation using the same volumetric analysis as in the present study (Akcali et al., 2015). SCTG were used to augment single pontic sites in the control groups and compared to the use of vascularized interpositional periosteal-connective tissue grafts in the test groups. Both treatment modalities were successful in augmenting soft tissue and resulted in an increase in soft tissue volume of 1.2 mm in the control group and 1.3 mm in the test group, respectively, from baseline to 3 months. Whereas no shrinkage was observed between 30 and 90 days after soft tissue augmentation for both treatment modalities, the control group lost almost half of the volume (47%) at the follow-up after 6 months. The volume in the test group, on the other hand, remained stable. This difference was explained with an impaired blood perfusion and integration of the graft in the control group, which may have led to an increased turn-over at the augmented site. Beside the biological processes, which occur over time as part of remodeling and maturation, the use of restorations may have an effect on dimensional soft tissue changes. In all of the already mentioned studies, which analyzed the volumetric changes after insertion of the final reconstructions, only minimal changes in soft tissue volume up to -0.15 mm one year after insertion were observed (Eghbali et al., 2014, Schneider et al., 2011, De Bruyckere et al., 2015). The mechanical stimulus caused by the reconstruction appears to positively influence the soft tissue stability. This is also in line with a recent report on pontic sites, demonstrating that over the course of 5 years following the insertion of a fixed tooth-borne reconstruction, almost no volume changes were evident, irrespective of whether or not the pontic areas had previously been augmented with SCTGs (Sanz-Martin et al., 2016).

Up to date, there is only limited data from clinical studies in terms of the effectiveness of soft tissue substitutes for oral soft tissue volume augmentation with varying results and reported gain in thickness of up to 2.14 mm (Batista et al., 2001,

Simion et al., 2012). The present findings are in line with the results of a previous preclinical study comparing the same treatment modalities (SCTG and VCMX) in chronic ridge defects (Thoma et al., 2010). In that study, a statistically significant increase in soft tissue thickness (for VCMX and SCTG) without significant differences between the groups was observed 30 days post surgery. In addition, a shrinkage between 30 days and 90 days post-surgery was identified corresponding to the results of present study. Apart from favorable tissue integration, the use of VCMX resulted in a soft tissue volume increase non-inferior to the SCTG. The results, however, should be interpreted with caution due to a number of limitations associated with the study design. This included: variations in graft thickness, number of treated patients and the definition of the regions of interest. Indications for soft tissue grafting in the present study varied and primarily included subjective criteria such as volume deficiency. This implied that the sites varied in terms of location, pre-existing soft tissue thickness and the amount of connective tissue that could be harvested (in case of the SCTG group). From a clinical point of view, all sites were augmented with a graft dimension that was considered appropriate to obtain the desired outcome. Based on this subjective criterion, no standardization was possible in terms of the amount of transplanted soft tissue (SCTG or VCMX) and the pre-existing soft tissue thickness might have further influenced the outcome. The technique used to assess the volume changes is well documented in the literature. The chosen ROIs were standardized as much as possible, but are limited due to variations between the sites that did not allow using the same ROI in all cases. In addition, the study also indicated that the applied sample size calculation underestimated the differences between sites and patients even though a 30% drop-out rate was included. Future studies might include a higher number of patients to support and underline the results obtained in the present study.

CONCLUSIONS

The use of the volume-stable collagen matrix for soft tissue augmentation at implant sites resulted in a non-inferior increase of soft tissue volume compared to the use of an autogenous subepithelial connective tissue graft. Within the limitations of this study VCMX and SCTG can be used for soft tissue augmentation at implant sites resulting in a at least short-term increase in soft tissue volume.

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FIGURE LEGENDS

Figure 1:

Clinical procedures represented with cases (left: VCMX=volume-stable collagen matrix; right: SCTG = subepithelial connective tissue graft). a. Clinical situation at screening. b. VCMX/SCTG on top of the ridge and underneath the buccal flap. c. Primary wound closure. d. Follow-up examination at 90 days (FU-90) e. Abutment placed. f. Final reconstruction in situ (not part of the present study).

Figure 2:

a. The crestal region of interest (ROI) represented a trapezoid shape and was located at the crestal aspect of the grafted area including the area between the midcrestal line and the gingival margin of the adjacent teeth. b. The buccal ROI represented a trapezoid shape and was located at the buccal aspect of the grafted area, starting at the gingival margins of the adjacent teeth and extending apically to the mucogingival border and laterally to interproximal areas. Due to the individually variable anatomical situations, the measured area varied between patients, but was kept constant in each patient and site over time.

Figure 3:

a. Outline of the superimposed baseline (yellow), 30 days (FU-30; white), and 90 days (FU-90, green) models in the central section of the grafted area (left: VCMX=volume-stable collagen matrix; right: SCTG = subepithelial connective tissue graft). b. 3D-reconstruction of the baseline model (yellow) and the volumetric changes in the crestal ROI between baseline and FU-90 (orange)

Table 1A: Patient demographics and p-values (Mann-Whitney test). SD=standard deviation. Min=minimum. Max=maximum. VCMX=volume-stable collagen matrix. SCTG=subepithelial connective tissue grafts.

Table 1B: Location and number of augmented sites for each group. VCMX=volume-stable collagen matrix. SCTG=subepithelial connective tissue grafts.

Table 2: Change in soft tissue thickness and p-values (Wilcoxon-signed rank test for within group and Mann-Whitney test between the groups). VCMX=volume-stable collagen matrix. SCTG=subepithelial connective tissue grafts. FU-30=Follow-up at 30 days. FU-90=Follow-up at 90 days. SD=Standard deviation. Q1=25th percentile. Q3=75th percentile.

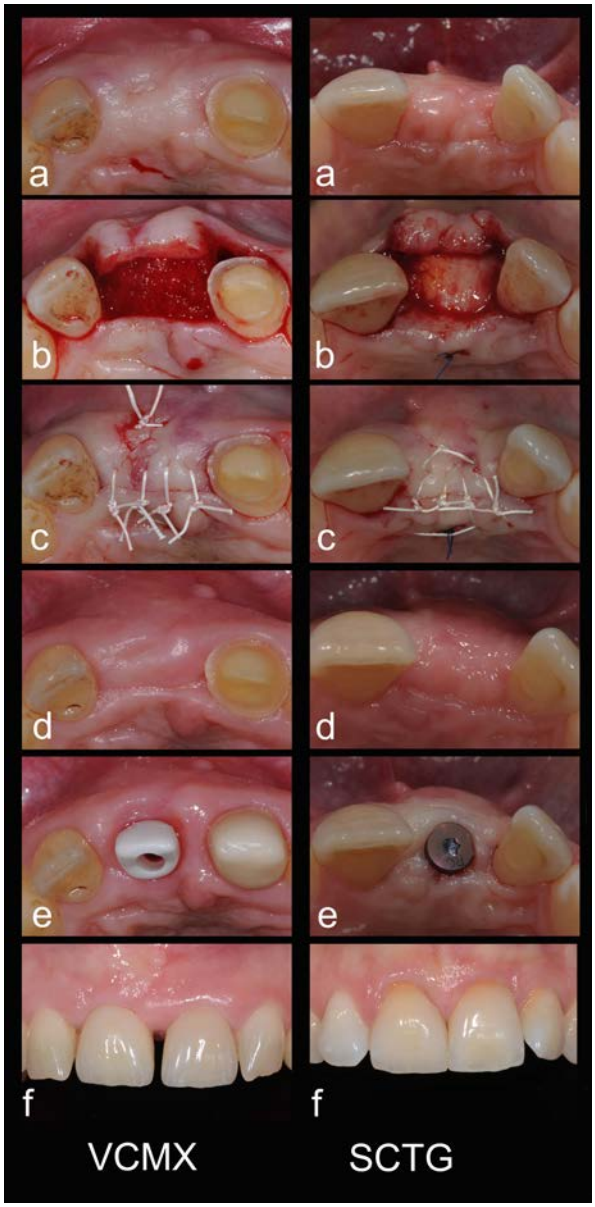

Figure 1

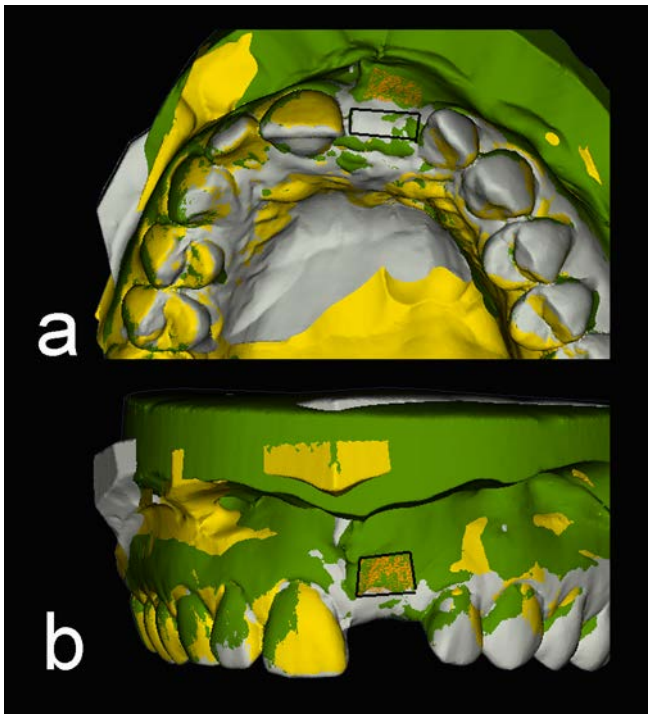

Figure 2

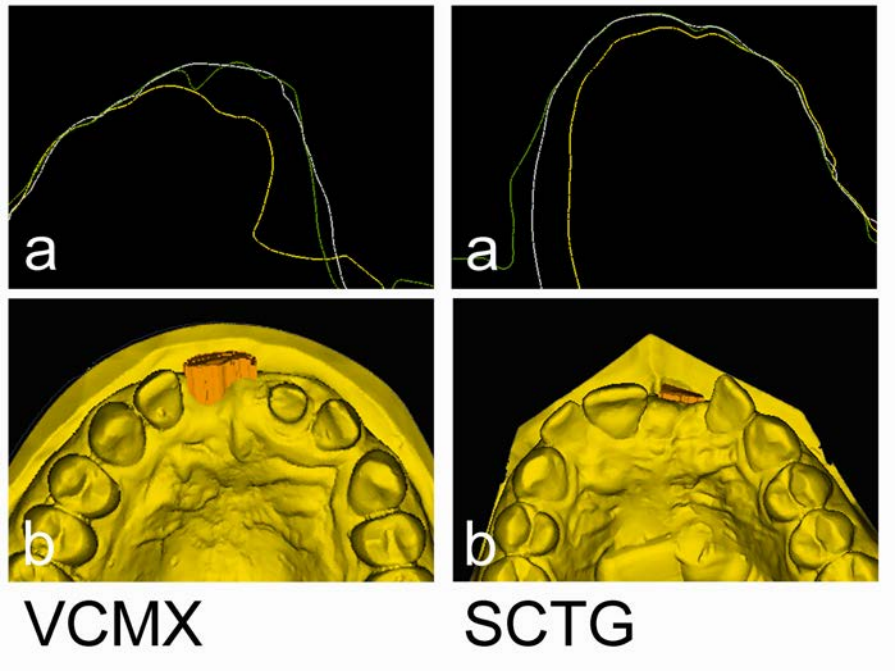

Figure 3

Table 1

		VCMX (n=10)	SCTG (n=10)	p-value
Gender	n (female) n (male)	7 3	6 4	1.000
Age	Mean SD Median Q1 ; Q3	43.8 13.2 45.0 39.1 ; 47.8	42.7 19.1 46.7 22.4 ; 60.1	1.000
Cigarettes per day	Mean SD Median Q1 ; Q3	0.8 2.5 0.0 0.0 ; 0.0	1.0 2.5 0.0 0.0 ; 0.0	1.000

Table 2

Site	15	14	13	12	11	21	22	23	24	25
VCMX	1				3	2			1	3
SCTG				2	2	4	1			

Site	45	44	43	42	41	31	32	33	34	35
VCMX										
SCTG						1				

Table 3

		VCMX [mm]				SCTG [mm]				
		n	Mean ± SD	Median (Q1 ; Q3)	p-value within group	n	Mean ± SD	Median (Q1 ; Q3)	p-value within group	p-value between groups
Baseline to FU-30	crestal	10	0.56 ± 0.41	0.41 (0.24 ; 0.94)	0.002	9	0.66 ± 0.68	0.53 (-0.02 ; 1.24)	0.055	0.826
	buccal	10	1.16 ± 0.72	1.10 (0.54 , 1.68)	0.002	9	1.05 ± 0.61	1.22 (0.59 ; 1.49)	0.004	0.968
Baseline to FU-90	crestal	10	0.27 ± 0.26	0.18 (0.06 ; 0.51)	0.002	9	0.42 ± 0.74	0.51 (0.23 ; 0.94)	0.129	0.287
	buccal	10	0.77 ± 0.74	0.59 (0.26 ; 1.06)	0.002	9	0.79 ± 0.45	0.94 (0.66 ; 1.13)	0.004	0.534
FU-30 to FU-90	crestal	10	-0.29 ± 0.24	-0.29 (-0.36 ; -0.21)	0.006	9	-0.24 ± 0.33	-0.19 (-0.31 ; -0.10)	0.055	0.675
	buccal	10	-0.39 ± 0.22	-0.44 (-0.59 ; -0.24)	0.002	9	-0.25 ± 0.26	-0.15 (-0.45 ; -0.09)	0.016	0.287